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L5 ANSWER 1 OF 7 CAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1994:215313 CAPLUS

DOCUMENT NUMBER: 120:215313

TITLE: Vicinal diol linking agents for antibody

fragments and therapeutic agents

INVENTOR(S): Frazier, Kevin A.; Schott, Margaret E.

PATENT ASSIGNEE(S): Dow Chemical Co., USA

SOURCE: U.S., 18 pp. Cont.-in-part of U.S. Ser. No.

478,286, abandoned.

CODEN: USXXAM

	NUMBER	DATE
		<b>-</b>
PATENT INFORMATION:	US 5274119 A	931228
APPLICATION INFORMATION:	US 91-677936	910401
PRIORITY APPLN. INFO.:	US 88-214247	880701
	US 90-478286	900209
DOCUMENT TYPE:	Patent	

DOCUMENT TYPE: Patent LANGUAGE: English

OTHER SOURCE(S): MARPAT 120:215313

AB A group of functionalized linking agents are disclosed. The linking agents contain thiol-reactive functionalities for covalent reaction with sulfhydryl groups from the hinge region of antibody fragments. The linking agents also contain masked aldehyde functionalities for covalent attachment of amine-contg. therapeutic agents by Schiff base formation. Carrier systems capable of delivering compds. to targeted sites in vivo based on antigen-antibody interactions are constructed from these linking agents. Thus, maleimido linking agent I was prepd. and used to further prep. a Fab-105Rh

chelate mol. Prepn. of the chelate [105Rh complex

with 6-(4-aminophenyl) methyl-1,4,8,11-tetraazoundecane] is also included.

L5 ANSWER 2 OF 7 CAPLUS COPYRIGHT 1996 ACS ACCESSION NUMBER: 1994:128617 CAPLUS

DOCUMENT NUMBER: 120:128617

TITLE: An improved linker for single-chain Fv with reduced aggregation and enhanced proteolytic

08/541,191 Page 3

stability

AUTHOR(S): Whitlow, Marc; Bell, Brian A.; Feng, Sheau Line;

Filpula, David; Hardman, Karl D.; Hubert, Steven

L.; Rollence, Michele L.; Wood, James F.;

Schott, Margaret E.; et al.

CORPORATE SOURCE: Protein Eng. Dep., Enzon, Inc., Piscataway, NJ,

08854-3998, USA

SOURCE: Protein Eng. (1993), 6(8), 989-95

CODEN: PRENE9; ISSN: 0269-2139

DOCUMENT TYPE: Journal LANGUAGE: English

The effects of linker length on binding affinity and degree of aggregation have been examd. in the antifluorescein 4-4-20 and anticarcinoma CC49 single-chain Fvs. Longer linkers in the antifluorescein sFvs have higher affinities for fluorescein and aggregate less. A proteolytically susceptible site between Lys8 and Ser9, in the previously reported 212 linker has been identified. new linker sequence, 218 (CSTSGSGKPGSGEGSTKG) was designed in which a proline was placed at the C-terminal side of the proteolytic clip site in the 212 linker. The CC49 sFv contg. the 218 linker showed reduced aggregation and was found to be more stable to proteolysis in vitro, when compared to the CC49/212 sFv. The CC49 sFv with the longer 218 linker had higher affinity than CC49/212 sFv. An aggregated CC49/212 sFv sample had higher affinity than CC49/218 The CC49/218 and CC49/212 sFvs had similar blood clearances in mice, while the aggregated CC49/212 sFv remained in circulation significantly longer. In mice bearing LS-174T human colon carcinoma xenografts, the CC49/218 sFv showed higher tumor uptake than the CC49/212 sFv and lower tumor uptake than the aggregated CC49/212 sFv. The higher tumor uptake of the CC49/218 is most likely a result of its higher resistance to proteolysis. The higher affinity and higher tumor uptake of the aggregated CC49/212 sFv are most likely due to the repetitive nature of the TAG-72 antigen and the higher avidity of multivalent aggregates. When the sFvs were radiolabeled with a lutetium-chelate the CC49/218 sFv showed a lower accumulation in the liver and spleen compared to the aggregated CC49/212 sFv.

L5 ANSWER 3 OF 7 CAPLUS COPYRIGHT 1996 ACS ACCESSION NUMBER: 1993:55232 CAPLUS

DOCUMENT NUMBER: 118:55232

TITLE: Differential metabolic patterns of iodinated

versus radiometal chelated

anticarcinoma single-chain Fv molecules

AUTHOR(S): Schott, Margaret E.; Milenic, Diane

E.; Yokota, Takashi; Whitlow, Marc; Wood, James

F.; Fordyce, William A.; Cheng, Roberta C.;

Schlom, Jeffrey

CORPORATE SOURCE: Lab. Tumor Immunol. Biol., Natl. Cancer Inst.,

Bethesda, MD, 20892, USA

SOURCE: Cancer Res. (1992), 52(22), 6413-17

CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal LANGUAGE: English

AB Genetically engineered single-chain Fvs (sFv) are defined as recombinant proteins composed of a variable light chain amino acid sequence of an Ig tethered to a variable heavy chain sequence by a designed peptide. Previous studies using iodine-labeled sFv, derived from the anticarcinoma monoclonal antibody CC49, showed that the 125I-sFv could efficiently target antigen-pos. tumors in a human tumor xenograft model while demonstrating rapid plasma clearance and

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minimal uptake in normal organs. One of the issues raised in the anal. of the iodinated sFv metabolic studies was whether similar metabolic patterns would be obsd. if the sFv were labeled with a radiometal. In the studies reported here, 125I-CC49 sFv and 177Lu-CC49 sFv were coinjected in mice bearing antigen-pos. human carcinoma xenografts. Both sFv forms showed similar tumor targeting and plasma clearance pharmacokinetics. The 177Lu-sFv, however, showed a greater uptake in liver and spleen and a much higher uptake in kidney. These studies thus demonstrate that despite their small size (Mr 27,000), the metal-chelated sFv shows a metabolic pattern very different than that of the iodinated sFv, which is most likely due to retention of the metal by organs metabolizing the sFv.

L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1983:610522 CAPLUS

DOCUMENT NUMBER: 99:210522

TITLE: Intracellular injections of EGTA block induction

of hippocampal long-term potentiation

AUTHOR(S): Lynch, Gary; Larson, John; Kelso, Stephen;

Barrionuevo, German; Schottler, Frank

CORPORATE SOURCE: Cent. Neurobiol. Learn. Mem., Univ. California,

Irvine, CA, 92717, USA

SOURCE: Nature (London) (1983), 305(5936), 719-21

CODEN: NATUAS; ISSN: 0028-0836

DOCUMENT TYPE: Journal LANGUAGE: English

AB Intracellular injection of the Ca2+ chelator EGTA blocked the development of long-term potentiation in slices of rat hippocampus; however, there were no detectable effects on the resting membrane potential, membrane impedance, or the excitatory postsynaptic potential amplitude before high-frequency stimulation. Possibly, EGTA, by buffering intracellular Ca2+, prevents the activation of the enzyme machinery controlling postsynaptic receptors and thereby blocks the induction of long-term potentiation.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 1996 ACS ACCESSION NUMBER: 1973:466454 CAPLUS

DOCUMENT NUMBER: 79:66454

TITLE: Silicon complexes. VII. Chelate

complexes of silicon with keto enolates and

similar ligands

AUTHOR(S): Schott, G.; Golz, Karin

CORPORATE SOURCE: Sekt. Chem., Univ. Rostock, Rostock, E. Ger. SOURCE: Z. Anorg. Allg. Chem. (1973), 399(1), 7-24

CODEN: ZAACAB

DOCUMENT TYPE: Journal LANGUAGE: German

AB RSiCl3 (R = Me, CH2:CH, ClCH2, Ph) reacted HL (HL = acetylacetone, benzoylacetone, dibenzoylmethane, and benzoylacetanilide) to give [RSiL2]+Cl-, which were easily converted into [RSiL2]+X- (X = HCl2-, FeCl4-, SnCl5-). The latter fact and ir and uv data indicated the ionic character of the complexes with penta-coordinated Si. [SiL3]+Cl-[HL1 = 2-hydroxyacetophenone, 1-nitroso-2-naphthol, 2-nitroso-1-naphthol, and Bz(Ph)NOH], [SiL13]+HCl2-, SiL12Cl2, and ClCH2SiL12X1 (X1 = Cl- HCl2-) were obtained from SiCl4 or ClCH2SiCl3 and HL1.

L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 1996 ACS ACCESSION NUMBER: 1971:476909 CAPLUS

DOCUMENT NUMBER: 75:76909

Silicon complexes. V. Chelate TITLE: complexes of monoorganotrihalosilanes with .beta.-diketones Schott, G.; Golz, Karin AUTHOR(S): Sekt. Chem., Univ. Rostock, Rostock, Ger. CORPORATE SOURCE: Z. Anorg. Allg. Chem. (1971), 383(3), 314-20 SOURCE: CODEN: ZAACAB DOCUMENT TYPE: Journal LANGUAGE: German MeSiFC12 and RSiC13 (R = Me, C1CH2, Ph) reacted with HL (HL = acetylacetone, benzoylacetone, dibenzoylmethane) to give [RSiL2]+ which were isolated as the chloride, HCl2-, FeCl4-, SnCl5-, and picrate. The complexes were characterized by ir and uv spectra. ANSWER 7 OF 7 CAPLUS COPYRIGHT 1996 ACS 1970:21741 CAPLUS ACCESSION NUMBER: 72:21741 DOCUMENT NUMBER: Silicon complexes. IV. Formation of TITLE: chelate complexes of silicon with ethyl benzoylacetate Schott, Guenther; Kibbel, H. U.; AUTHOR(S): Hildebrandt, W. Univ. Rostock, Rostock, Ger. CORPORATE SOURCE: Z. Anorg. Allg. Chem. (1969), 371(1-2), 81-7 SOURCE: CODEN: ZAACAB DOCUMENT TYPE: Journal LANGUAGE: German SiCl4, RSiCl3, RSiCl2(OAc), R2SiCl2, or R3SiCl (R = Me, Et) react with BzCH2CO2Et (HL) to give (SiL3)HCl2, RSiL2Cl, RSiL2(OAc), R2SiL2, and R3SiL, resp., which were characterized by uv and ir spectroscopy. => s 15 and dota 195 DOTA L70 L5 AND DOTA => s 15 and dota? 309 DOTA? 0 L5 AND DOTA? , L8 => s 15 and dtpa? 5142 DTPA? 0 L5 AND DTPA? L9 => d his (FILE 'HOME' ENTERED AT 12:24:09 ON 17 SEP 96) FILE 'CAPLUS' ENTERED AT 12:24:16 ON 17 SEP 96 0 S SCHOTT/AU L11532 S SCHOTT?/AU L2 5135 S L2 AND DOTA OR DTPA L3 0 S L2 AND (DOTA OR DTPA) L47 S L2 AND CHELAT? L5 0 S L5 AND RADIO ISOTOP? L6 0 S L5 AND DOTA L7 0 S L5 AND DOTA? L8 0 S L5 AND DTPA? 1.9

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30988 DIAMINE?